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Can the preoperative HE4 level predict optimal cytoreduction in patients with advanced ovarian carcinoma?

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HIGHLIGHTS

- HE4 is a better predictor for optimal cytoreduction compared with CA125.
- HE4 ≤ 262 pmol/L and ascites <500 mL have a sensitivity of 100% and a specificity of 89.5% in predicting cytoreduction.

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ABSTRACT

Objective. Optimal surgical outcome has been proved to be one of the most powerful survival determinants in the management of ovarian cancer patients. Actually, for ovarian cancer patients there is no general consensus on the preoperatively establishment of cytoreducibility.

Methods. Between January 2011 and June 2012 patients affected by suspicious advanced ovarian cancer, referred to the Department of Gynecology of Campus Biomedico of Rome were enrolled in the study. All patients had serum CA125 and HE4 measured preoperatively. After a complete laparoscopy to assess the possibility of optimal debulking surgery defined as no visible residual tumor after cytoreduction (RT = 0), patients were submitted to primary cytoreductive surgery (Group A) or addressed to neoadjuvant chemotherapy (Group B).

Results. After diagnostic open laparoscopy, 36 patients underwent optimal primary cytoreductive surgery (Group A) and 21 patients were addressed to neoadjuvant chemotherapy (Group B). In our population, based on ROC curve, the HE4 value of 262 pmol/L is the best cut-off to identify patients candidates to optimal cytoreduction with a sensitivity of 86.1% and a specificity of 89.5% (PPV = 93.9% and NPV = 77%). In addition, CA125 has a sensitivity of 58.3% and a specificity of 84% at cut-off of 414 UI/mL (AUC is 0.68, 95% C.I. = 0.620 to 0.861).

Conclusion. Our data indicate that preoperative HE4 is a better predictor for optimal cytoreduction compared to CA125. The best combination in predicting cytoreduction is HE4 ≤ 262 pmol/L and ascites <500 mL with a sensitivity of 100% and a specificity of 89.5% (PPV = 94% and NPV = 100%).

Introduction

Surgical cytoreduction followed by platinum–taxane chemotherapy is the cornerstone of management of patients with advanced ovarian carcinoma. Optimal surgical outcome has been proved to be one of the most powerful survival determinants [1]. More specifically each 10% increase in maximum or optimal cytoreduction rate prolonged median cohort survival by 5.5% [2].

The degree of residual disease is the only factor that can be addressed by the surgeon.

The definition of "optimal" has changed over time, from residual tumor (RT) <2 cm diameter of the largest nodule, to the current no macroscopical residual tumor load. [2,3]. However, a certain percentage of women, ranging between 25% and 90% [1,4], is not susceptable to be optimally cytoreduced and should be addressed to neoadjuvant chemotherapy; hence, the need to address the ideal timing of cytoreduction has assumed greater clinical importance.

Actually, there is no general consensus about the best way to preoperatively establish the cytoreducibility of ovarian cancer patients.

Laparotomy constitutes the most accurate way to evaluate tumor burden and establish whether or not a patient is suitable of optimal surgery. However, it is an aggressive approach if used only to assess tumor resectability and it can postpone the start of chemotherapy [5].

Some authors have suggested the positive role of diagnostic laparoscopy to predict surgical outcome in patients with advanced ovarian carcinoma with an overall accuracy rate that ranges between 77.3% and 100%

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[5,6]. On the other hand, the preoperative laboratory assessment of operability is based mainly on abdomen and pelvis computed tomography (CT-scan) and CA125 serum levels. CT-scan can effectively identify omental infiltration, hepatic or splenic metastases, peritoneal thickening, ascites, lymph node enlargement, and ovarian tumor characteristics, but to date controversy still exists regarding its ability to predict their resectability [7–9]. Several studies have addressed the issue of a CA125cut-off above which chances for optimal primary cytoreduction are limited, and therefore, the surgical intervention should be postponed. Most of them indicate CA125 level of 500 U/ml as the proper cut-off limit for this purpose, but yet some others find that the method cannot reliably predict optimal cytoreduction [10–21]. Therefore, the development of novel biomarkers that can sufficiently contribute to predicte cytoreducibility is paramount in identifying specific patients who may benefit from primary debulking surgery. Many studies have suggested that serum HE4 is useful for the detection of ovarian cancer with a sensitivity of 76.9% [22] and in ovarian cancer recurrence [23], its prognostic role has not been determined. Up to now, there are no studies on HE4 role in predicting optimal tumor cytoreduction of epithelial ovarian cancer. Aim of our study is to evaluate if preoperative HE4 is a good predictor for optimal cytoreduction in advanced ovarian cancer and to determine the cut-off level with the maximum prognostic power.

Materials and methods

Between January 2011 and June 2012 consecutive patients affected by suspicious advanced ovarian cancer, referred to the Department of Gynecology of Campus Biomedico of Rome were prospectively enrolled in the study.

Inclusion criteria were: performance status <2 according to WHO criteria, age above 18 years, good nutritional status, no contraindications to surgery, preoperative Computed Tomography (CT) with evidence of extra pelvic disease and ability to provide informed consent.

Exclusion criteria were: patients with non-epithelial, mucinous or borderline cancers, pathology consistent with primary peritoneal or fallopian tube carcinoma, neoadjuvant chemotherapy, stages I–II, previous major abdominal surgery and/or radiotherapy.

All patients had serum CA125 and HE4 measured preoperatively.

The measurement of serum CA125 was made with the standard radio-immunoassay (normal limits<35 IU/ml) during the entire study period.

HE4 levels were determined using the HE4 EIA assay (Fujirebio Diagnostics). The HE4 EIA is a solid phase, non competitive immunoassay based upon the direct "sandwich" technique using two monoclonal antibodies, 2H5 and 3D8, directed against two epitopes in the C-WFDC domain of HE4 [23].

The day before surgery all patients underwent to transvaginal ultrasonography to measure by the three largest perpendicular diameters (width, length and depth) the largest fluid pockets in the pelvis, in order to assess if ascites was present (<500 ml or>500 ml).

To measure the intraperitoneal volumes we use the formula:

$$y(mL) = -4 \times 10^{-8}V^4 + 4 \times 10^{-5}V^3 - 1.32 \times 10^{-2}V^2 + 2.45V + 34,217$$

where V is the volume calculated by adding the volume of each identifiable pocket approximated to the volume of a cube (D1 x D2 x D3, where D1, D2 and D3 represent the maximal height, length, and width of the pocket in centimeters) [24].

All patients underwent diagnostic laparoscopy in order to assess the possibility of optimal debulking surgery defined as no visible residual tumor after cytoreduction (RT = 0).

After a complete laparoscopic exploration of the pelvis and abdomen with a careful visualization of the ovaries, fallopian tubes, uterus, pelvic peritoneum, serosa and mesentery of the large and small bowel, liver surface, paracolic gutters and diaphragm and an aspiration of peritoneal fluid, patients were submitted to either laparotomy and primary cytoreductive surgery (Group A) through a midline xifo-pubic incision or were closed and addressed to neoadjuvant chemotherapy (Group B).

Reasons for submitting patients to neoadjuvant chemotherapy instead of primary debulking surgery included factors related to the extent of the disease (surgical findings at diagnostic open laparoscopy). In particular, surgical findings influencing the allocation of the patient in Group B were: extended visceral peritoneal metastases, large involvement of upper abdomen, extended small bowel involvement, multiple liver metastases, heavily bleeding tumoral tissue. For extended visceral peritoneal metastasis, we meant diffuse superficial involvement of organs such as small bowel, large bowel, liver, gallbladder. For large involvement of upper abdomen, we meant tumor involving both diaphragm and liver, or liver hilum. For extended small bowel involvement, we meant multiple sites superficial and/or deep (thin and/or apparently thick) small bowel metastases [5].

Primary debulking surgery of Group A patients consisted in total hysterectomy, bilateral salpingo-oophorectomy with comprehensive staging

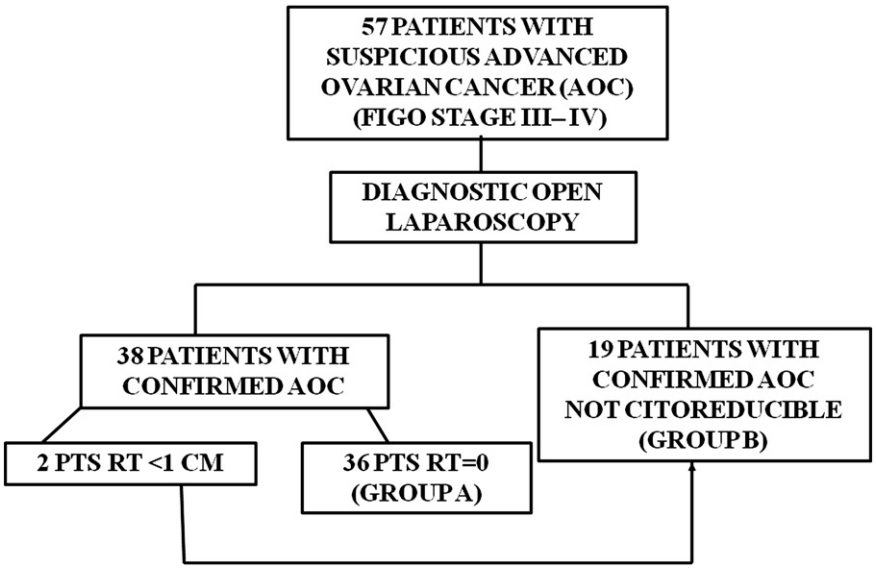

Fig. 1. Consort trial flow diagram.